This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 21!

See attached form for additional information.

Interagency Report Control No.:

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. CERTIFICATE NUMBER: 22-R-0009
CUSTOMER NUMBER: 519

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

Novartis Pharmaceuticals Corporation
Bldg 437/1329 One Health Plaza
East Hanover, NJ 07936

Telephone: (973) -781-0074

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Atached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (**Attach additional sheets if necessarv or use APHIS Form 7023A**)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not ye used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use o pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals an for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reasc such drugs were not used must be attached to this report	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs	105	283	11	36	330
5. Cats					
6. Guinea Pigs		3			3
7. Hamsters		10			10
8. Rabbits	17	620		29	649
9. Non-human Primates	332	546	7	173	726
10. Sheep					
11. Pigs					
12. Other Farm Animals					
13. Other Animals					
14. Gerbil		10			10

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anestetic, analgesic, and tranquilizing drugs, prior to, during, and following actual rese teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and ap Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary inc brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL

(b)(6), (b)(7)c

DATE SIGNED 12-3-07

4/C19

USDA ANNUAL REPORT OF RESEARCH FACILITY FOR 2006-2007
NOVARTIS PHARMACEUTICALS CORPORATION
USDA Registration No. 22-R-0009

Summary of the NACUC approved exceptions to the Standards and Regulations:
Canine Exercise Exemptions

Protocol Title	Species	Number	Days Without Exercise	Reason
1. Evaluation of Pharmacokinetic and Pharmacodynamic Properties of Compounds in Dogs	Dogs	1	40	Prescribed rest following adverse reaction to dosing
2. Evaluation of Pharmacokinetic and Pharmacodynamic Properties of Compounds in Dogs	Dogs	1	9	Prescribed rest following adverse reaction to dosing
3. Absorption, Distribution, Metabolism, and Excretion After A Single Oral or IV Dose in the Dog	Dogs	1	19	Radioactive isolation
4. Absorption, Distribution, Metabolism, and Excretion After A Single Oral or IV Dose in the Dog	Dogs	5	8	Radioactive isolation
5. Absorption, Distribution, Metabolism, and Excretion After A Single Oral or IV Dose in the Dog	Dogs	5	7	Radioactive isolation
6. Training, Development and Refinement of Procedures	Dogs	1	30	Prescribed rest following surgery

USDA ANNUAL REPORT OF RESEARCH FACILITY FOR 2006-2007
NOVARTIS PHARMACEUTICALS CORPORATION
USDA Registration No. 22-R-0009

Summary of the NACUC approved exceptions to the Standards and Regulations:
Canine Exercise Exemptions

Protocol Title	Species	Number	Days Without Exercise	Reason
7. Effects of Antihypert. Comp on BP Resp.to Vasoactive Agents in Concious Dogs	Dogs	1	12	Prescribed rest following surgery
8. Effects of Antihypert. Comp on BP Resp.to Vasoactive Agents in Concious Dogs	Dogs	1	5	Prescribed rest following surgery

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 20. Number of animals classified as category "E" - 13.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Eleven monkeys experienced dermatological effects. One monkey experienced dermatological effects and was humanely euthanized. One monkey experienced the compound related effect decreased locomotor activity.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

As soon as there were signs that one animal was experiencing significant pain and distress it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 4. Number of animals classified as category "E" - 1.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

One monkey experienced dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animal remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 32. Number of animals classified as category "E" - 3.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Three monkeys experienced compound related effects, primarily diarrhea and dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 18. Number of animals classified as category "E" - 1.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

One monkey experienced dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animal remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 10. Number of animals classified as category "E" - 3.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Two monkeys experienced compound related effects, primarily decreased locomotor activity. One monkey experienced compound related effects, primarily decreased locomotor activity and was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs for two monkeys were not severe and euthanasia was not necessary, therefore the animals remained on study.

As soon as there were signs that one animal was experiencing significant pain and distress it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 32. Number of animals classified as category "E" - 12.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

One monkey experienced dermatological effects and was humanely euthanized. One monkey experienced the compound related effect decreased locomotor activity and was humanely euthanized. Five monkeys experienced the compound related effect diarrhea for at least 3 days and were humanely euthanized. Three monkeys experienced the compound related effect diarrhea for at least 3 days. Two monkeys experienced dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs for five monkeys were not severe and euthanasia was not necessary, therefore the animals remained on study.

As soon as there were signs that animals were experiencing significant pain and distress they were euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 30. Number of animals classified as category "E" - 15.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Eight monkeys experienced compound related effects, primarily dermatological effects and decreased locomotor activity. Five monkeys experienced dermatological effects. One monkey experienced the compound related effect decreased locomotor activity. One monkey experienced the compound related effect decreased locomotor activity and was sacrificed unscheduled.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs for fourteen monkeys were not severe and euthanasia was not necessary, therefore the animals remained on study.

As soon as there were signs that one animal was experiencing significant pain and distress it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

> 1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 30. Number of animals classified as category "E" - 24.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Twenty-four monkeys experienced dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 10. Number of animals classified as category "E" - 5.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Four monkeys experienced compound related effects, primarily emesis. One monkey experienced dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 40. Number of animals classified as category "E" - 27.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Twenty-six monkeys experienced dermatological effects. One monkey experienced dermatological effects and was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

One animal was treated but due to significant pain and distress was humanely euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 10. Number of animals classified as category "E" - 9.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Nine monkeys experienced the compound related effect decreased locomotor activity.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 24. Number of animals classified as category "E" - 10.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Ten monkeys experienced dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The animals were treated and the clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 12. Number of animals classified as category "E" - 5.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Four experienced dermatological effects. One monkey experienced dermatological effects and was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs for four monkeys were not severe and euthanasia was not necessary, therefore the animals remained on study.

As soon as there were signs that one animal was experiencing significant pain and distress it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 4. Number of animals classified as category "E" - 2.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

One monkey presumably experienced compound related effects and expired. One monkey experienced compound related effects, primarily impaired motor abilities.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animal remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 10. Number of animals classified as category "E" - 6.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Three monkeys experienced compound related effects, primarily diarrhea for at least 3 days. Two monkeys experienced diarrhea for at least 3 days and decreased locomotor activity. One monkey experienced diarrhea for at least 3 days and decreased locomotor activity and was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

Five animals were treated and the clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

As soon as there were signs that one animal was experiencing significant pain and distress it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 2. Number of animals classified as category "E" - 2.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Two monkeys experienced compound related effects, primarily impaired motor activity.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 32. Number of animals classified as category "E" - 3.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Two monkeys experienced the compound related effect decreased locomotor activity. One monkey experienced dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 18. Number of animals classified as category "E" - 7.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

One monkey presumably experienced compound related effects and expired. Two monkeys experienced dermatological effects. Four monkeys experienced decreased locomotor activity and dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 36. Number of animals classified as category "E" - 7.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

One monkey presumably experienced compound related effects and expired. One monkey experienced recumbency and swelling was humanely euthanized. One monkey experienced decreased locomotor activity and abdominal distention. Four monkeys experienced swollen limbs.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs for five animals were not severe and euthanasia was not necessary, therefore the animals remained on study.

As soon as there were signs that one animal was experiencing significant pain and distress it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 12. Number of animals classified as category "E" - 2.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Two monkeys experienced compound related effects, primarily dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The animals were treated and the clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 16. Number of animals classified as category "E" - 7.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Seven monkeys experienced compound related effects, primarily diarrhea for at least 3 days.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The animals that experienced diarrhea for at least 3 days were treated. The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study – 46. Number of animals classified as category "E" - 9.

3. Species (common name)___Non-human Primate___ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These primates were dosed with a pharmaceutical compound.

Seven monkeys experienced compound related effects, primarily emesis. One monkey experienced diarrhea for at least 3 days and emesis as a compound related effect. One monkey experienced diarrhea for at least 3 days as a compound related effect.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The animals that experienced diarrhea for at least 3 days were treated. The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 6. Number of animals classified as category "E" - 3 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

Three dogs experienced compound related effects in this study, primarily decreased locomotor activity and were humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that the animals were experiencing pain or distress, they were euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 6 . Number of animals classified as category "E" - 1 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

One dog experienced dermatological effects.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animal remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 14 . Number of animals classified as category "E" - 1 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

One dog was misdosed and was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that the animal was experiencing pain or distress, it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 14 . Number of animals classified as category "E" – 3* .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

One dog experienced compound related effects in this study, primarily decreased locomotor activity, ataxia and muscle tremors and was humanely euthanized. One dog experienced compound related effects, primarily decreased locomotor activity and ataxia. One dog experienced compound related effects, primarily muscle tremors.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that the animal was experiencing pain or distress, it was euthanized.

The clinical signs for two animals were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

*- One animal listed as a Category E on this form was also listed as a Category E on another study

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 32 . Number of animals classified as category "E" - 8 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

Seven dogs experienced compound related effects in this study, primarily diarrhea at least days. One dog experienced compound related effects and was sacrificed unscheduled.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs for seven dogs were not severe and euthanasia was not necessary, therefore the animals remained on study.

As soon as there were signs indicating that one animal was experiencing pain or distress, it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 4 . Number of animals classified as category "E" - 1 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

One dog experienced compound related effects, primarily decreased locomotor activity.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animal remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 8. Number of animals classified as category "E" - 5 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

Five dogs experienced compound related effects in this study, primarily diarrhea.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 10. Number of animals classified as category "E" - 3 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

One dog experienced compound related effects in this study, primarily decreased locomotor activity and expired. One dog experienced compound related effects in this study, primarily decreased locomotor activity and was humanely euthanized. One dog experienced compound related effects in this study, primarily diarrhea and weight loss.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that the animal was experiencing pain or distress, it was euthanized.

The clinical signs for one animal were not severe and euthanasia was not necessary, therefore the animal remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 4 . Number of animals classified as category "E" - 1 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

One dog experienced compound related effects, primarily decreased locomotor activity and muscle tremors and was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that the animal was experiencing pain or distress, it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 32 . Number of animals classified as category "E" - 1 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

One dog experienced compound related effects in this study, primarily diarrhea for at least 3 days.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animal remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 32 . Number of animals classified as category "E" - 3 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

Two dogs experienced compound related effects in this study, primarily diarrhea at least three days. One dog experienced compound related effects and was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs for two dogs were not severe and euthanasia was not necessary, therefore the animals remained on study.

As soon as there were signs indicating that one animal was experiencing pain or distress, it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 4 . Number of animals classified as category "E" - 2 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

Two dogs experienced compound related effects in this study, primarily decreased locomotor activity and were humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that the animal was experiencing pain or distress, it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 9 . Number of animals classified as category "E" - 3 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

Three animals experienced adverse reactions to dosing.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The animals were treated and the clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 8 . Number of animals classified as category "E" - 1 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These dogs were dosed with a pharmaceutical compound.

One animal experienced adverse reactions to dosing and was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that the animal was experiencing pain or distress, it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 9 . Number of animals classified as category "E" - 1 .

3. Species (common name)____Dog_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

This dog was dosed with a pharmaceutical compound.

One animal experienced adverse reactions to dosing.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

This animal was treated and the clinical signs were not severe and euthanasia was not necessary, therefore the animal remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 98 . Number of animals classified as category "E" - 1 .

3. Species (common name)____Rabbit_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These rabbits were dosed with a pharmaceutical compound.

One rabbit experienced rales was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that this animal was experiencing pain or distress, it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

2) Guideline on detection of toxicity to reproduction for medicinal products published in the Federal Register on September 22, 1994 (FR 48746).

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 27 . Number of animals classified as category "E" - 2 .

3. Species (common name)____Rabbit_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These rabbits were dosed with a pharmaceutical compound.

Two rabbits experienced compound related effects and were humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that an animal was experiencing pain or distress, it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

2) Guideline on detection of toxicity to reproduction for medicinal products published in the Federal Register on September 22, 1994 (FR 48746).

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 30 . Number of animals classified as category "E" - 2 .

3. Species (common name)____Rabbit_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These rabbits were dosed with a pharmaceutical compound.

Two rabbits experienced compound related effects, primarily ataxia.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

2) Guideline on detection of toxicity to reproduction for medicinal products published in the Federal Register on September 22, 1994 (FR 48746).

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 30 . Number of animals classified as category "E" - 3 .

3. Species (common name)____Rabbit_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These rabbits were dosed with a pharmaceutical compound.

Two rabbits experienced compound related effects and expired. One rabbit experienced compound related effects and was humanely euthanized.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that an animal was experiencing pain or distress, it was euthanized.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

2) Guideline on detection of toxicity to reproduction for medicinal products published in the Federal Register on September 22, 1994 (FR 48746).

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 98 . Number of animals classified as category "E" - 5.

3. Species (common name)____Rabbit_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These rabbits were dosed with a pharmaceutical compound.

Five rabbits presumably experienced compound related effects and expired.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

2) Guideline on detection of toxicity to reproduction for medicinal products published in the Federal Register on September 22, 1994 (FR 48746).

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 30 . Number of animals classified as category "E" - 9 .

3. Species (common name)____Rabbit_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These rabbits were dosed with a pharmaceutical compound.

One rabbit experienced compound related effects and expired. Three rabbits presumably experienced compound related effects and were humanely euthanized. Five rabbits experienced compound related effects to the neurological system.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

As soon as there were signs indicating that an animal was experiencing pain or distress, it was euthanized.

The clinical signs for five rabbits were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

2) Guideline on detection of toxicity to reproduction for medicinal products published in the Federal Register on September 22, 1994 (FR 48746).

OPTIONAL COLUMN E EXPLANATION FORM

(b)(4)

1. Registration Number: 22-R-0009

2. Number of animals used in this study: 30 . Number of animals classified as category "E" - 7 .

3. Species (common name)____Rabbit_____ of animals used in this study.

4. Explain the procedure producing pain and/or distress.

These rabbits were dosed with a pharmaceutical compound.

Seven rabbits experienced compound related effects including ataxia and decreased activity.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see question 6 below)

The clinical signs were not severe and euthanasia was not necessary, therefore the animals remained on study.

6. What, if any, federal regulations require this procedure? Cite the agency, the Code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

The general reference is 21 CFR 312.23(a)(8). This reference indicates that there are guidelines available from the FDA that describe ways in which these requirements may be met. More specific guidelines may be found in the following:

1) M3 Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals published in the Federal Register on November 25, 1997 (62 FR 62922)

2) Guideline on detection of toxicity to reproduction for medicinal products published in the Federal Register on September 22, 1994 (FR 48746).